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| 10/813,249 | 03/30/2004 | Anna Depicker | 2676-6388US | 4486 |

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| EXAMINER | |
|---|---|
| MEHTA, ASHWIN D | |
| ART UNIT | PAPER NUMBER |
| 1638 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/813,249 | DEPICKER ET AL. | |
| | Examiner | Art Unit | |
| | Ashwin Mehta | 1638 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-10 and 13* is/are pending in the application.

4a) Of the above claim(s) *13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05172007* and 05102007
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. The amendment filed May 10, 2007 was entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The objection to the specification for referring to an incorrect figure number is moot, in light of the amendment.

4. The rejections of claims 1-12 under 35 U.S.C. 112, second paragraph, are withdrawn in light of the claim amendments or after consideration of Applicants' arguments.

5. The rejection of claims 1-12 under 35 U.S.C. 112, first paragraph is withdrawn in light of the claim amendments, or in consideration of Applicants' arguments.

### *Priority*

6. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 365(c), as certified copies of PCT/EP02/11188 and EPO 01203760.2 have not been filed.

In the paper filed May 10, 2007, Applicants indicate that the certified copies of the priority documents have been ordered and will be provided as soon as possible (page 5). Applicants' intent is acknowledged. The benefit of the filing dates of the priority documents cannot be granted until the copies are received.

***Claim Objections***

7. Claim 1 is objected to because of the following informalities: the term, "homolgous" in line 8 is misspelled. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

8. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1: the recitation, "the target gene comprises a region of at least 23 contiguous nucleotides that are at least 60% homolgous with the recombinant gene, but has no significant homology with the silenced locus" renders the claim, and those dependent thereon, indefinite. The recitation does not clearly indicate whether the target gene as a whole does not have significant homology with the silenced locus, of if it is just the region of at least 23 nucleotides that does not have significant homology with the silenced locus.

Further in claim 1: it is unclear if, on the recombinant gene, the region of at least 23 contiguous nucleotides that are at least 60% homologous with the silenced locus can overlap with, or whether is its location distinct from, the region that has at least 23 nucleotides that are at

least 60% homologous with the target gene. Given the explanation of the constructs of the invention on pages 6-8 and the diagrams in Figures 1-4, it is suggested that claim 1 be amended by inserting, --first-- in line 5 before "region", and in line 8 by inserting --a second region in-- before "the recombinant gene".

In claims 3-6: the recitation, "wherein the RNA silencing of the target gene is obtained more than 95% (or 85%) of the time in the host" renders the claims indefinite. The recombinant gene would have to be introduced into multiple hosts to determine if silencing of the target gene is obtained 95% or 85% of the time in the host. However, parent claim 1 indicates that the recombinant gene was introduced into "a" (one) host.

9. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the claimed method when the recombinant gene comprises a region of at least 23 nucleotides that are identical to the silenced locus, and when the target gene comprises a region of at least 23 nucleotides that are identical to the recombinant gene, does not reasonably provide enablement for the claimed method when the regions of homology are 23 nucleotides having less than 100% identity. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is broadly drawn towards a method for obtaining RNA silencing of a target gene comprising: introducing a recombinant gene into a host (plants are the elected species) comprising an RNA-silenced locus and the target gene, wherein the recombinant gene comprises a region of at least 23 nucleotides that are at least 60% homologous with the silenced locus, and

the target gene has a region of at least 23 nucleotides that are at least 60% homologous with the recombinant gene, but has no significant homology with the silenced locus, thus RNA silencing the target gene.

Paragraph [0010] of the specification states, "No significant homology means that either the overall homology is less than 40, 35, 30, 25% or even less or that no contiguous stretch of at least 23 identical nucleotides are present". Thomas et al., 2001 (Plant J., Vol. 25, pages 417-425) is cited at the end of this statement. Thomas et al. teach that a nucleic acid molecule of minimal 23 nucleotides in size and having 100% identity with a target mRNA is required for it to cause post-transcriptional silencing of that target mRNA (pages 418-419). Instant claim 1 states that the recombinant gene comprises a region of at least 23 nucleotides that are at least 60% homologous with the silenced locus, and the target gene has a region of at least 23 nucleotides that are at least 60% homologous with the recombinant gene. This encompasses regions that do not comprise at least 23 contiguous nucleotides that are identical to the silenced locus or recombinant gene. The recombinant gene and target gene in the working example in the specification contain regions of more than 23 contiguous nucleotides that have complete identity to the silenced locus and recombinant gene, respectively. In the absence of further guidance showing how these regions of homology can have less than 23 contiguous nucleotides of complete identity and retain the ability to cause post-transcriptional gene silencing of a target gene, undue experimentation would be required by one skilled in the art to make and use the claimed invention.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Houdt et al. (Mol. Gen. Genet., 2000, Vol. 263, pages 995-1002) in combination with Depicker et al. (Curr. Op. Cell Biol., 1997, Vol. 9, pages 373-382).

Claim 1 is broadly drawn towards a method for obtaining RNA silencing of a target gene comprising: introducing a recombinant gene into a host (plants are the elected species) comprising an RNA-silenced locus and the target gene, wherein the recombinant gene comprises a region of at least 23 nucleotides that are at least 60% homologous with the silenced locus, and the target gene has a region of at least 23 nucleotides that are at least 60% homologous with the recombinant gene, but has no significant homology with the silenced locus, thus RNA silencing the target gene; claim 2 limits the host of the method of claim 1 to comprising plant cells (elected species is plants); claims 3-10 require the RNA silencing of the target gene to be obtained more than 95% or 85% of the time in the host, or to occur at an efficiency of more than 95% or 85% ac compared to the level of the unsilenced expression of the target gene.

Van Houdt et al. teach plants comprising a T-DNA inverted repeat locus (HOlo1) showing PTGS of the neomycin phosphotransferase II (nptII) transgene, and plants comprising a T-DNA insert expressing nptII genes (HOlo2). nptII genes newly introduced into leaves of HOlo1 were silenced, whereas they were expressed when introduced into HOlo2 leaves

(abstract; page 997). Chimeric GUS genes comprising parts of the nptII transgene showed reduced expression only in the nptII-silenced HOlo1 leaves (abstract; page 998). The silenced nptII gene in the HOlo1 plants is an "RNA-silenced locus in the host plant. The nptII gene sequence in the chimeric GUS gene is a region comprising at least 23 nucleotides that are identical to the nptII gene (the RNA-silenced locus) in the HOlo1 plant. The chimeric GUS gene can be considered to be a "recombinant gene", as referred to in instant claim 1.

Claim 1 requires introducing a recombinant gene into a host that comprises an RNA-silenced locus and the target gene. The HOlo1 plant of Van Houdt et al. contains an RNA-silenced locus. Van Houdt et al. do not teach a host plant comprising a target gene before introduction of the recombinant gene.

Depicker et al. review PTGS in plants, assert that it depends on homology between silencing sequences, often between transgenes and homologous endogens; that homology-dependent gene silencing suppresses expression of homologous gene *in trans* (pages 373-374).

It would have been obvious and within the scope of one of ordinary skill in the art at the time the invention was made, that replacement of the GUS coding sequence in the recombinant gene of Van Houdt et al. with that of a gene already present in the host plant, would have caused the RNA silencing of that gene in the host plant. It was well established in the prior art that introduction of transgenes into plants causes the PTGS of their homologous endogenes, as reviewed by Depicker et al. Van Houdt et al. demonstrate that the initially RNA-silenced nptII locus in the HOlo1 plant lead to RNA silencing of the GUS coding sequence present in the chimeric GUS gene, because of the presence of the homologous region of nptII nucleotide

sequences in the chimeric GUS gene. If any other sequence other than GUS was used, it would have been silenced. If such an alternative transgene was a gene endogenous to the host plant, there would have been a reasonable expectation that the endogenous gene in the host plant would have been RNA-silenced as well, especially given that it was known in the art that homology-dependent gene silencing suppresses expression of homologous gene *in trans*. Alternatively, introduction and expression of a GUS coding sequence in the HOlo1 host plant of Van Houdt et al., before introduction of the chimeric GUS gene, would have lead to the RNA silencing of GUS expression both from the chimeric GUS construct, and from the initially introduced GUS sequence, with a reasonable expectation of success, given the knowledge of the PTGS pathway in the prior art at the time of filing. Van Houdt et al. demonstrate that RNA silencing of GUS occurred in all repeats of their experiment (page 998), indicating that RNA of silencing occurs in more than 95% or more than 85% of the time in the host. It was also obvious that RNA silencing of the target gene could occur at an efficiency of more than 85 or 95% as compared to the level of the unsilenced expression of the target gene, given the level of GUS silencing achieved by Van Houdt et al. (Table 1). It was obvious that percent of reduction in expression of the product encoded by the target depends not only on the PTGS mechanism, but also on the initial level of expression of the target gene (which also depends on its transcription control elements) in the absence of the recombinant gene.

11. Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Van Houdt et al. (Plant Physiol., 2003, Vol. 131, pages 245-253). This reference is available as prior art because the claim for priority in the instant application has not been perfected.

Claim 1 is broadly drawn towards a method for obtaining RNA silencing of a target gene comprising: introducing a recombinant gene into a host (plants are the elected species) comprising an RNA-silenced locus and the target gene, wherein the recombinant gene comprises a region of at least 23 nucleotides that are at least 60% homologous with the silenced locus, and the target gene has a region of at least 23 nucleotides that are at least 60% homologous with the recombinant gene, but has no significant homology with the silenced locus, thus RNA silencing the target gene; claim 2 limits the host of the method of claim 1 to comprising plant cells (elected species is plants); claims 3-10 require the RNA silencing of the target gene to be obtained more than 95% or 85% of the time in the host, or to occur at an efficiency of more than 95% or 85% ac compared to the level of the unsilenced expression of the target gene.

Van Houdt et al. teach the silencing of a target gene in plants. Three constructs were produced: "X", harboring an inverted repeat of the ntpII gene and the 3'-signaling sequence of the chalcone synthase (chs) gene of snapdragon; "Y", harboring a GUS gene containing the 3' chs sequence; and "Z", harboring a GUS gene having the 3' sequence from the nopaline synthase gene (Figure 1). Expression of the ntpII gene is post-transcriptionally silenced in plants comprising X (page 247), which can be considered an "RNA-silenced locus" in such plants. GUS expression is stable in plants comprising Y or Z alone (page 247). In plants comprising X and Y, expression of GUS was RNA-silenced. The homology shared between the X and Y constructs was mainly in the 3' chs sequence, and also in a small sequence of shared 29 nucleotides in the 5' UTR (page 247). GUS activity in XZ plants was normal. XY plants were crossed to Z plants to obtain plants harboring X, Y, and Z (page 252). GUS expression was silenced in these plants (page 247; Table 1).

Claim 1 requires introducing a recombinant gene into a host that comprises an RNA-silenced locus and the target gene. In Van Houdt et al., a target gene (on construct Z) was introduced into a plant comprising an RNA-silenced locus (construct X) and a recombinant gene (construct Y). Van Houdt et al. do not teach a host plant comprising a target gene before introduction of the recombinant gene.

It would have been obvious and within the scope of one of ordinary skill in the art to modify Van Houdt et al. by introducing the Y construct into a host plant comprising constructs X and a target gene. An XZ host plant would have an RNA-silenced locus (for nptII) on X, and a target gene, the GUS coding sequence, on Z. It would have been obvious that subsequent introduction of construct Y (the recombinant gene) would have resulted in RNA silencing of the GUS coding sequence (the target gene) on Z, and the GUS coding sequence on Y. Van Houdt et al. explain that it is the stepwise homology between the constructs that resulted in silencing of the GUS sequence on Z and Y in plants comprising all three constructs (pages 247-248). Therefore, it was obvious that the presence of the target gene in the host plant comprising X, before introduction of construct Y, would not have affected the eventual RNA-silencing of the target gene. Table 1 indicates that RNA silencing efficiency of the target gene in XYZ plants was more than 95% as compared to the level of its unsilenced expression. The percentage of host plants, including more than 85% or 95%, showing RNA silencing of the target gene can depend on the total number of plants used.

12. Claims 1-10 remain rejected, claim 13 remains withdrawn.

***Contact Information***

Any inquiry concerning this or earlier communications from the Examiner should be directed to Ashwin Mehta, whose telephone number is 571-272-0803. The Examiner can normally be reached from 8:00 A.M to 5:30 P.M. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Anne Marie Grunberg, can be reached at 571-272-0975. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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August 3, 2007

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